



Report to CIA Research Committee

Genetic Testing Model for CI: If Underwriters of Individual Critical Illness Insurance Had No Access to Known Results of Genetic Tests

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Memorandum

To: CIA Research Committee

From: Robert C. W. (Bob) Howard, FCIA, FSA

Date: January 12, 2016

Subject: Genetic Testing Model for CI: If Underwriters of Individual Critical Illness

Insurance Had No Access to Known Results of Genetic Tests

The Research Committee engaged me to construct a model to assess the impact on companies and the public if underwriters were prohibited from accessing the results of genetic tests known to applicants. I was to consider individual critical illness insurance (CI) only. This is a follow-up engagement to the earlier one for life insurance. The genetic assumptions were to be provided by a committee of doctors and underwriters assembled by the Canadian Life and Health Insurance Association (CLHIA), but otherwise my modelling was to be independent of the CLHIA and member companies.

The Research Committee appointed a research project management team (RPMT) chaired by Bernard Naumann and including Alison Begley, Paul Fryer, and Benoit Miclette, all Fellows of the Canadian Institute of Actuaries. My work was supervised by the RPMT. Both method and assumptions were discussed with the RPMT at length.

This document is a report on my work: a description of the model, method, and assumptions; my observations from the modelling; and my conclusions about the impact on the insuring public of Canada.

RCWH



1 Executive Summary

Consideration is being given in some legislative bodies in Canada to prohibiting life insurance companies from accessing the results of genetic tests known by the applicant for the purpose of underwriting a potential insured. Such an action would create an imbalance of information between the applicant and the insurance company. This report describes a model that explores the impact of the prohibition on the premiums paid by Canadians. The model considers six conditions that are known to be associated with a genetic marker and for which reasonable estimates of their effect on critical illness insurance (CI) claims are known. The model simulates the purchase of insurance, exposure, and CI claims separately for each condition.

The key assumptions, other than those related to the rate of claim under the six conditions, are what proportion of those who test positive will seek to buy CI and how much will they buy. The baseline assumption in the model is that 75% of those who test positive will apply for \$250,000 of insurance, and the rest will not seek additional insurance. The greater the publicity surrounding the prohibition, the higher will be the proportion buying CI.

I conclude that the impact on insurance companies will be material, although less than for life insurance. As a result of the prohibition the average CI claim rates are likely to increase by about 26% overall, or 16% for males and 41% for females, in the age range 30–65; there would be a concomitant increase in CI premium rates.

It is important to note that the results are highly dependent on the assumptions, particularly the amount of insurance sold to those who test positive, whether through each purchasing a larger amount or a higher proportion seeking insurance.

One can quickly test the impact of the key anti-selective assumptions as they are relatively proportional. That is, if one assumes only 50% of those who test positive will apply for \$250,000 of insurance, then the impact will be close to two thirds (i.e. 50% / 75%) of the overall 26% impact, or 17%. Similarly, if one assumes 75% of those who test positive will apply for only \$100,000 of insurance, then the impact will be close to 40% (i.e. \$100,000 / \$250,000) of the overall 26% impact, or 10%.

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3 Introduction

In our society, genetic tests are becoming increasingly affordable and accessible. This is good for the public because people are able to determine whether they are prone to certain serious conditions. Knowing that they have a high probability of an illness often improves the outcomes thanks to closer monitoring and lifestyle changes before the illness becomes manifest. Of course, the presence of a particular gene does not, in most cases, indicate that the person has the disease currently; there remains uncertainty about if and when the disease will emerge.

For many of the more serious conditions, those who test positive for the gene or genes associated with the condition will recognize that their likelihood of claim is markedly increased compared to the rest of the population. It would be logical for them to want to acquire additional insurance, particularly if it can be had at a favourable price.

Some European countries have enacted legislation to make the results of genetic tests inaccessible to underwriters of insurance. Consideration has been given in some Canadian legislative bodies to doing the same. If insurance underwriters are not permitted to know the results of genetic tests that are known to the applicants, then many of those who test positive will be able to acquire CI (and life insurance) at the same price as those who are untested or test negative.

The purpose of my model is to explore the actuarial implications of an enforced imbalance of genetic information (the applicant may know it, but the underwriter may not) and to determine whether there is likely to be a material impact on the individual CI market in Canada.

4 Model Specifications

4.1 Overview

My model simulates the purchase of CI policies in one year by those who test positive for any of a number of genetic markers and follows the policies for many years. The totals for these policies are compared to the totals for a block of standard issues of CI similar to what is sold in a year in the absence of a ban (the normal block). The impact of the ban is estimated by comparing the experience for both blocks combined to the normal block alone. The comparison is limited to attained ages 30 to 65 because these are the main ages for purchase of CI.

My model simulates individual CI only, without the return of premium provision.

A similar study has been done for individual life insurance. See References.

4.2 Assumptions about Genetic Markers

The assumptions related to the genetic markers were provided by a committee of medical doctors and chief underwriters drawn by the Canadian Life and Health Insurance Association (CLHIA) from its member companies. I have had further discussions with the doctors. I am not qualified to make these assumptions myself. I have relied on but do not take responsibility for the assumptions set out below in table

1 as the consensus of the doctors. (This is a disclosure in accordance with 1610.02 of the Standards of Practice. It does not imply any objection to the assumptions.) From my discussion with the doctors and my knowledge of their expertise, I am comfortable using their work.

The references supporting the assumptions are shown in appendix 3, table 4.

4.2.1 Conditions Included

There are more than 5,000 genes that have been identified as relating to illnesses, and more are being discovered daily. In some cases, a single gene is associated with a disease; in other cases it is a combination of two or more genes. Only a few have been studied in sufficient detail to establish a quantitative link between the gene and the rate of mortality or morbidity. Fewer still are known to have a direct impact on a listed condition in a typical CI policy. Genes that have an indirect impact on CI conditions or that have no studies with a sufficient number of cases that would have qualified as a CI claim are excluded. In particular most cardiac genes, other than dilated cardiomyopathy (DCM), are not included here; the outcome is most commonly sudden death rather than a CI claim. DCM is included because some cases result in strokes or being on a waiting list for a heart transplant.

Table 1 shows the six conditions that were chosen for inclusion in my model. They are listed below with the abbreviations that appear in table 1 shown in parentheses.

- Breast cancer (BRCA);
- 2. Lynch syndrome, also called hereditary nonpolyposis colorectal cancer (Lynch);
- 3. Dilated cardiomyopathy (DCM);
- 4. Blindness;
- 5. Polycystic kidney disease (PKD); and
- 6. Alzheimer's disease early onset autosomal dominance (ADEO).

Table 1. Conditions included and associated assumptions for the model									
Condition	Prevalence	Penetrance	Claim	Predicted	Test Low	Test High	Male	Clm Age	Std Dev
BRCA	1000	50%	90%	50%	20	45	0%	45	5
Lynch	500	50%	50%	25%	20	45	50%	55	5
DCM	2700	75%	10%	25%	20	35	50%	40	5
Blindness	5000	90%	100%	75%	20	25	50%	35	6
PKD	1000	100%	90%	75%	25	40	50%	60	10
ADEO	2427	100%	100%	50%	30	40	50%	57	10

4.2.2 Prevalence

The prevalence of the genetic marker in the Canadian population is expressed as 1 per n.

BRCA is an exception. Although it is found in both males and females at about 1 in 500, prevalence is shown as 1 in 1,000 because it is assumed that few males will perceive

their risk of cancer being elevated enough to have different motivation for purchase or a higher likelihood of claim than normal purchasers.

4.2.3 Penetrance

Penetrance is defined as the probability that those with a particular gene will ultimately develop the disease. Not all with the genetic marker will develop the disease. Some will die or claim first due to other causes. Studies of penetrance are of limited duration; some may develop the disease at an older age. Penetrance is expressed as a percentage of those who have the gene. The complement of penetrance is assumed to be standard risks. It is important to note the division into these two groups, penetrance and its complement (referred to as substandard and standard), is an artifact of the model. An individual would not know in which group he or she belonged until symptoms appeared indicating membership in the substandard group.

4.2.4 Claim

Those with the disease will exhibit a higher rate of CI claim. The "claim" parameter represents the percentage of the substandard group who will ultimate qualify for a CI claim, provided they have not lapsed or claimed of some other cause or died.

4.2.5 Predicted

Some of those with the gene will be identified by the underwriting process from family history or early symptoms of the disease even if the results of the genetic test are not disclosed. This is expressed as a percentage. Thus if "predicted" is shown as 25%, it is assumed that 25% of those who test positive will be identified by the underwriter and rated, and 75% will obtain insurance at standard rates. For simplicity, the factors were chosen in 25% intervals.

Given that the family history questions refer to genetic disorders, one might think that the underwriting process would be very successful in identifying those who might carry a gene of concern. However, because the questions are limited to parents and siblings and because it is common to have only one or no siblings, it is not infrequent that there is no sign of the disorder in family history although the gene is present.

4.2.6 Test Low and Test High

These two numbers give an age range for those who test positive. The distribution of testing is assumed to be uniform over this interval. In fact, the distribution is unknown. It is not likely to be uniform, and there are likely to be some tested outside the specified age range. However, I believe that the use of a limited, uniform distribution is sufficiently representative to give reasonable, unbiased results.

4.2.7 Male

This is the proportion who are male. Breast cancer is assumed to apply to females only. All other conditions are equally distributed by gender.

4.2.8 "Clm Age" and "Std Dev"

These are the average age at claim and the standard deviation in the age at claim. Unlike the other assumptions in this section, I proposed the standard deviations to the doctors, and after discussion we agreed on numbers that seemed to produce a reasonable distribution of claim. The average age at claim is used in the model as the later of the specified number and five years after the age at testing.

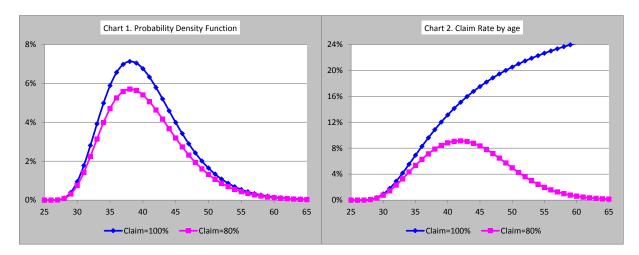
4.2.9 Distribution of Claim

I have assumed a gamma distribution for the number of years from testing to claim. I have no empirical evidence to support gamma as preferable to any other distribution. However, gamma has a number of advantages. The probability for negative values is zero. Probabilities are readily determinable for any combination of mean and standard deviation. The pattern of probabilities looks reasonable to the doctors who have had clinical experience with the diseases.

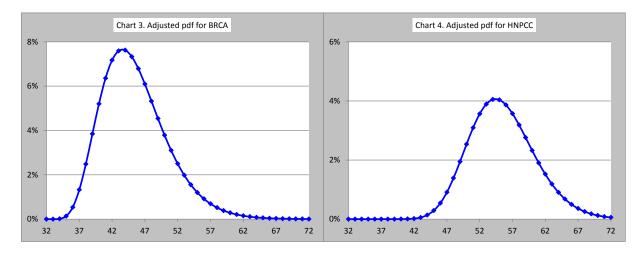
But not all who develop the disease (Penetrance) will satisfy the CI definition of claim (Claim). Therefore, the cumulative density function of the gamma distribution is multiplied by the Claim factor. The rate of claim in any year is then given by the following formula, in which "cdf" is for the gamma distribution, "Claim" is the Claim factor, x is the age at testing and t is the duration from testing.

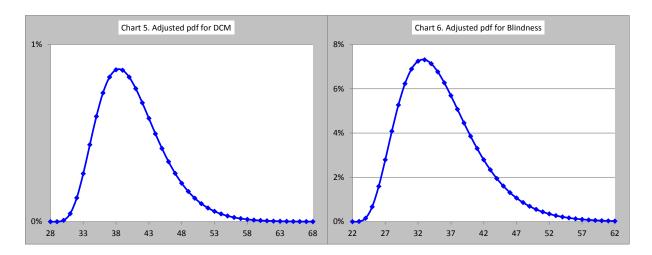
$$q_{[x]+t-1} = \frac{Claim(cdf_t - cdf_{t-1})}{1 - Claim \, cdf_{t-1}}$$

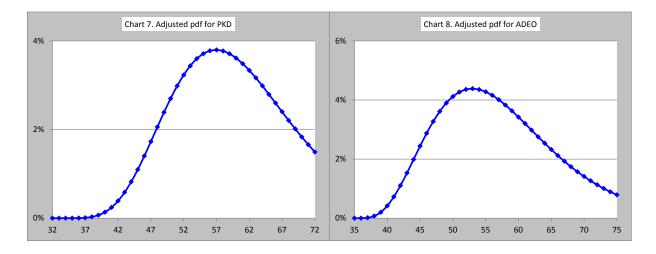
Chart 1 below shows the impact of varying Claim on a probability density function (probability of claim in each year for those with penetrance). The effect is intuitive. Chart 2 is less intuitive and much more interesting. It shows the rate of claim in each year based on the above formula and varying Claim. When Claim is 100%, the rate of claim increases with duration and becomes very high in later years. When Claim is less than 100%, the rate of claim increases initially but later decreases; those who have survived with the disease for several years become less likely to claim eventually.



Charts 3 to 8 show the probability density functions for each of the six conditions included in the model. Note that all charts begin with the average age at testing and run for 40 years; both the horizontal and vertical scales may differ for each chart.







4.3 Other Assumptions

4.3.1 Population

The population is assumed to be 35 million.

4.3.2 Testing Rate

It is assumed that those in the population who have one of the genes are tested at a uniform rate of 1/30 per year; thus, all with the gene will be tested over a generation. It is expected that there will be some event that precipitates the call for testing, such as a family member being diagnosed with the condition. Then siblings, children, and probably cousins and others would be encouraged to be tested to determine whether they also have a propensity for the condition.

4.3.3 Seeking Insurance

Those who test positive will likely learn very soon through genetic counsellors, the media, and disease support groups that life insurance companies are prohibited from asking for the results of the genetic test. They will then know that they can obtain CI at the same price as most others in the population, which they know to be favourable to them because of their increased probability of claim. Most are likely to buy CI for any of a variety of reasons:

- 1. To provide for their care when the disease emerges;
- 2. To offset a loss of income during illness; and/or
- 3. To take advantage of the superior ratio between cost and benefit.

The proportion seeking insurance would certainly not be 100%, but it could be close. It would tend to increase as the prohibition gains publicity, particularly among interest groups supporting those with the diseases related to the positive tests. The assumption used is 75%, with one exception.

Dilated cardiomyopathy (DCM) is the exception. Because the likelihood of a life insurance claim is much greater than the likelihood of a CI claim for DCM, it is assumed that only 50% will seek CI. (The assumed proportion claiming is only 10% of those who test positive and eventually develop the disease. DCM is included as a representative of heart-related genes; its impact on the overall cost is negligible. Of course, some with DCM may buy both life insurance and CI.)

4.3.4 Declined

It is assumed that 10% of applicants are declined for reasons unrelated to the conditions under study. The same rate of decline is used for both the standard and the substandard groups. It is typical for an insurance company to decline about 14% of CI applicants, but most of those are at higher ages than the assumed age at testing. Accordingly 10% is reasonable for the ages who test positive.

4.3.5 Mortality

The mortality assumption is the same as used for standard mortality in the earlier study on life insurance.

Standard mortality is based on the CIA 97–04 table for non-smokers, age nearest birthday. The table is multiplied by factors taken from the most recently published study of the CIA, 72.7% for male select, 71.8% for female select, 80.1% for male ultimate, and 87.7% for female ultimate. To these mortality rates, four years (2010 to 2014) of mortality improvement are applied using the CIA Committee on Life Insurance Financial Reporting scale. No future mortality improvement assumption is assumed.

4.3.6 Morbidity

The standard CI claim rates were obtained from two recent CIA publications, 2008 CANCI (publication #212059T) and the experience study of 2003–2011 (publication #214132). The experience study uses, as the expected table, the sum of the rates in 2008 CANCI for the benefits included in the policy exposed, and a proportion of the rates for benefits that have a partial payment. For the purpose of this model, the version of 2008 CANCI is the sum of the rates for all benefits, but only 15% of each of early stage malignant melanoma, early stage prostate cancer, ductal carcinoma in situ, and coronary angioplasty. (The industry average for partial payments is currently around 15%.)

As an aside, it could be argued that the sum of the incidence rates should be decreased to reflect the probability of satisfying the claim definition of more than one condition in the same year. However, because that is not done for the experience study, I did not do so either for consistency.

The effect of selection was obtained from table C5g (page 29) of the experience study. This table shows A/E ratios for each of durations 1–9 and for 10+ for males and females combined. I smoothed the ratios manually, and then applied the smoothed rates to my version of 2008 CANCI to calculate an incidence table separately by sex for issue ages 15 to 70 and durations 1–9 of select plus ultimate. Thus the highest incidence rate available is for attained age 79; if a rate is needed for a higher age, the rate for age 79 is used. (As the model is currently structured, rates over attained age 65 are not used.)

The substandard morbidity rates are described in section 4.2.9.

It is assumed that those who test positive for the gene can be divided into two groups based on penetrance: those who develop the disease (the penetrance percentage, referred to as substandard) and those who do not (one minus the penetrance percentage, referred to as standard). It is important to draw this distinction because all who test positive will be motivated to buy CI, but the substandard claim rates applies only to substandard. Of course, in reality one cannot know which group an individual will fall into, and not all in the standard group will exhibit standard morbidity.

All lives in the simulation are exposed to the standard CI claim rates. The substandard lives of the positive group are also exposed to the substandard CI claim rates for the appropriate gene.

The CI claims rates, both standard and substandard, do not change during the simulation; there is no improvement or deterioration.

4.3.7 Lapse

The lapse rate for all years is 0.5% for the substandard lives and 3% for standard lives. The lapse rate is higher for standard lives because they are more likely to abandon their insurance after no evidence of the disease for many years. It might be better to assume the lapse rate for standard starts out at 0.5% and gradually increases because individuals do not know initially whether they are in the standard or substandard group, but the flat assumption was used to simplify the model.

The lapse rate for the comparison group of normal issues of CI (without return of premium) is 4% in all years.

Lapse rates are applied at the end of each policy year; other decrements assume a uniform distribution of claims over the policy year.

4.3.8 Amount of Insurance

It is expected, based on the bills recently considered in legislatures, that the underwriters will have access to the results of genetic tests for amounts of insurance in excess of \$1 million. (In comparison the UK moratorium is capped at £500,000 for life insurance and £300,000 for CI.) Because CI is much more expensive than life insurance, those who test positive may apply for less than the maximum. Also the average amount in force for CI is about \$100,000 for males and \$80,000 for females. In comparison recent purchases of life insurance average about \$400,000 for males and \$300,000 for females. Because policies of \$1 million or more are much rarer for CI than for life insurance, the underwriter may question the justification for a very large policy. The assumed amount purchased is \$250,000.

It is also possible that the threshold for allowing access to the results of genetic tests could be set much lower than \$1 million. Section 5 includes chart 13, which shows how the impact on experience varies by the amount assumed to be purchased.

It is fairly common for a CI policy to include a "return of premium" provision. However, my model does not recognize this provision.

4.3.9 Sales of Base Group

The experience for the tested lives is compared to the experience for a base group. The base group represents the CI policies that would have been sold in the absence of a ban. The total volume of insurance assumed to be sold in one year is \$7.65 billion, the amount reported sold in 2014 by LIMRA. The age distribution is taken from the latest intercompany study of CI experience conducted by the CIA; consider duration 1 exposures only. The base group considers sales only for issue ages 20–69.

4.4 Method

The model simulates purchases of CI in one year by those who test positive for each condition (the positive group). The number of policies purchased for a condition is the population multiplied by the prevalence, multiplied by the proportion tested each year, multiplied by the proportion not declined, multiplied by 1 less the proportion predicted in underwriting. This number of policies is divided into four groups based on the assumed penetrance and gender: male substandard, male standard, female substandard, and female standard. Each is assumed to buy a policy for the assumed amount. The issue age is the same as the age at testing and is spread uniformly over the range of testing ages for that condition.

The model also simulates purchases in one year for a group of standard lives, very similar in amount and sex-age distribution to those who have recently purchased CI in Canada (the base group). The base group can be thought to contain only those who are untested or who test negative.

Each group is followed as a cohort of lives in a deterministic simulation for 40 years. The simulation notes, for each group and each condition and for each duration, the number of lives and amount of insurance in force and the number and amount of CI claims.

The purpose of the model is to estimate the difference in the CI experience between the base group and the sum of the base group and the positive group. One can expect that future studies of the CI experience by the CIA would show the impact of the two groups combined. (Of course, in the event of a ban, the positive group cannot be separated and studied separately because the insurance companies would not know who was tested.) The CIA experience study is important and is used as a significant factor by many companies in determining their CI claims assumption for pricing. If CI claim rates were to increase, or were expected to increase, because many substandard lives were being rated as standard, those increases would soon be reflected in general premium rates.

The exposure and CI claims for the two simulations were summarized for attained ages of 30 to 65 with duration not more than 40. These ages and durations are important for the purchase of insurance; those who test positive will typically be found more at the younger end of the range. The impact of the prohibition was measured as the increase in the A/E ratio (actually the simulated CI claims divided by the expected CI claims) for the sum of the two groups over that for the base group only.

5 Results of Model Runs

The overall impact on CI experience is an increase of 26%. The increase is substantially more for females (41%) than for males (16%). The reason is that only females are exposed to BRCA, which is the most significant condition, and that the base group is somewhat larger for males than for females so that the impact is leveraged more for females. The impact on premium rates is likely to be a little less than on claim rates.

Some may be surprised that the impact is so much less than shown in my earlier model for life insurance. There are two main reasons.

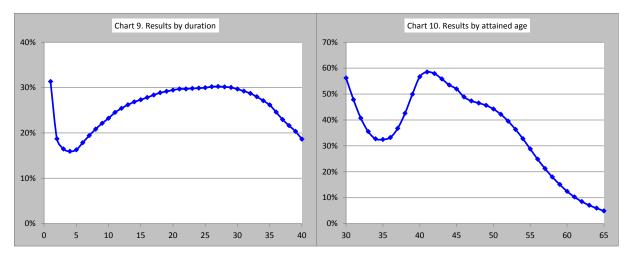
The first is that the genes with the largest impact for life insurance are highly likely to result in death but unlikely to result in a critical illness claim. The only heart-related gene in both studies is DCM. Some of those with DCM may suffer a stroke in the later stages, and a few may be healthy enough to qualify for a waiting list for heart transplant. Most are likely to die from heart failure before they satisfy the requirements for a CI claim. Other heart-related genes in the life insurance model are even less likely to claim for CI. The impact from blindness, the one gene included in this model that was not included for life insurance, is small.

The second is that the amount assumed to be purchased for CI of \$250,000 is substantially less than the \$900,000 assumed for life. What will determine the actual impact under a ban is the amount of insurance actually purchased by those who test positive. The assumption used for CI could be considered consistent with that for life because in both cases it is about 2.5 times the average amount currently purchased. On the other hand, if the ban has a maximum of \$1 million for both CI and life, as has been proposed, then the upward potential is much greater for CI than for life.

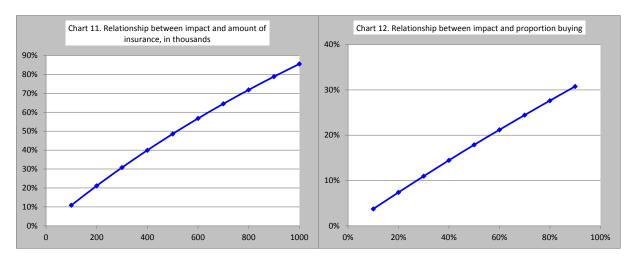
Table 2 shows the impact, for males and females combined, for each of the genes included in the model.

Table 2. Impact for each condition				
Condition	Impact			
BRCA	6.4%			
Lynch	9.4%			
DCM	0.4%			
Blindness	1.0%			
PKD	4.3%			
ADEO	4.5%			
Total	26.0%			

The impact varies considerably by duration and by age. Chart 9 shows the impact, for males and females combined, by duration, and chart 10 by attained age. Note that the impact by duration has a local minimum around duration 5 and a local maximum around duration 18. This pattern is caused by the fact that BRCA has an impact that tend to decrease with duration, but other genes have an increasing impact for several years.



The most important non-genetic factors in the model are the amount of insurance purchased and the proportion of those who test positive who decide to purchase. Chart 11 shows how the impact varies with the amount purchased; the relationship is not far off linear. Chart 12 shows how the impact varies the proportion buying; the relationship is very close to linear. (The calculations for chart 12 assume that the proportion buying for DCM is 50% or the overall proportion if less.)



The results shown are forward-looking in the sense that the impact on experience may be smaller initially, perhaps not even noticeable for a couple of years. Gradually the impact will become observable in traditional experience studies. Pricing actuaries may respond earlier if they accept this model and thus anticipate the trend in experience.

It is important to note that because I am modelling a situation that has not happened in Canada and because the medical information is still emerging, the assumptions are not precise, and hence, the results cannot be taken as precise.

6 Conclusions

The impact from not allowing underwriters to have access to the results of genetic tests known to the insurance applicant is material for CI; in my opinion the impact is

significantly more than insurance companies could be expected to absorb without an increase in premium rates.

As more genetic tests emerge for serious illnesses, it is likely that the impact will continue to grow. If the link between a particular illness and certain genes is especially strong, insurance companies may decide to withdraw that illness from their CI products as an uninsurable risk.

All of the preceding is predicated on the threshold for the ban being at \$250,000 of insurance or higher. If the threshold were set at \$100,000 for CI, which is slightly more than the average amount in force per CI policy, then the impact on premium rates would be much less, but likely not zero.

7 Limitations

My assignment was to construct a simple model that would be understandable to most actuaries. Due to my keeping the model simple, the results may be less representative of reality than would be the case for a more robust model. Nonetheless I believe that although the magnitude of the results might vary, the conclusions would not change materially.

Two possible enhancements are suggested below; both would tend to increase the impact. The enhancements would move the model toward what might be considered a higher level of accuracy, but the enhancements could not be considered cost-justified in the sense of having a large enough impact on the quantitative results that different qualitative conclusions would be reached.

- The assumptions for the genetic markers agreed to by the doctors were generally chosen to be at the lower end of any given ranges where such choices had to be made. Using neutral estimates would produce a larger impact.
- 2. As this model considers six out of thousands of genetic markers, more could be added. However, the list was chosen based on CI impact and availability of information.

8 Sensitivities

Table 3 shows the impact on the results of the model from changing any one of a variety of assumptions. The results for the base case are shown on the line "Base assumptions".

Table 3. Sensitivity to changes in assumptions						
Assumption	Total	Increase				
Base assumptions	26.0%	n/a				
Testing from 1/30 to 1/40	19.9%	-6.1%				
Proportion buying from 75% to 50%	17.9%	-8.2%				
Amount bought from 250k to 150k	16.1%	-9.9%				
Declined from 10% to 5%	27.4%	1.3%				
Substd lapse rate from 0.5% to 0	28.3%	2.3%				
Std lapse rate from 3% to 0.5%	25.5%	-0.5%				
Normal lapse rate from 4% to 3%	22.1%	-3.9%				

The results are strongly sensitive to the first three assumptions shown in table 3; further testing indicates that the results are nearly proportional to these assumptions. Charts 11 and 12 above illustrate a wider range of values for the assumptions on the proportion buying and the amount bought.

The sensitivity to the other assumptions is not nearly as strong.

Appendix 1. Review of Model

The CIA Report Project Management Team actively reviewed my assumptions and method as I built the model, made suggestions, and ultimately gave its approval.

The model was reviewed by another actuary, who found the work to be acceptable.

Appendix 2. References

Howard, Robert C. W. Report to CIA Research Committee: Genetic Testing Model: If Underwriters Had No Access to Known Results. Canadian Institute of Actuaries (CIA). July 10, 2014. http://www.cia-ica.ca/publications/publication-details/214082

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Macdonald, A. S., and F. Yu. "The Impact of Genetic Information on the Insurance Industry: Conclusions from the 'Bottom-Up' Modelling Programme". *ASTIN Bulletin,* 41 (2011), 343. http://www.macs.hw.ac.uk/~angus/papers/overall_impact.pdf

Appendix 3. References for Genetic Assumptions

Table 4 below contains references to documents supporting many of the genetic assumptions. These references were provided by the doctors who developed the assumptions.

Table 4: Genetic Assumptions and References						
Gene	Prevalence of gene mutation (1 in X)	Prevalence web reference	Penetrance of clinical expression given mutation positive	Penetrance web reference		
BRCA1 or 2	1000 (female only)	http://www.ncbi.nlm.nih.g ov/books/NBK1247/	50% (female only)	http://www.cancer.gov/ty pes/breast/hp/breast- ovarian-genetics- pdq#section/all		
Dilated cardiomyo- pathy 4%/yr	2700	http://www.ncbi.nlm.nih.g ov/books/NBK1309/	75%	http://www.ncbi.nlm.nih.g ov/pubmed/10400009		
Polycystic kidney disease	1000	http://www.uptodate.com /contents/diagnosis-of- and-screening-for- autosomal-dominant- polycystic-kidney- disease/abstract/3	100%	http://www.uptodate.com /contents/diagnosis-of- and-screening-for- autosomal-dominant- polycystic-kidney- disease/abstract/33		
Alzheimer's – autosomal dominance (100% penetrance bucket)	2427	http://omim.org/entry/104 300	100%	http://www.uptodate.com /contents/genetics-of- alzheimer- disease?source=machineLe arning&search=alzheimers &selectedTitle=2%7E150&s ectionRank=2&anchor=H65 62978#H6562978		
Colorectal cancer (Lynch)	500	http://www.ncbi.nlm.nih.g ov/books/NBK1211/	50%	http://www.ncbi.nlm.nih.g ov/books/NBK1211/		

Blindness	5000	http://www.ncbi.nlm.nih.g ov/books/NBK1417/	90%	http://www.medscape.co m/viewarticle/432579_5
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